

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Efficacy of Low-magnitude High-frequency Vibration (LMHFV) on Musculoskeletal Health of Participants on Wheelchair: A Study Protocol for A Single-blinded Randomized Controlled Study
<b>AUTHORS</b>	Chow, Simon Kwoon Ho; Ho, Chung Yan; Wong, Hiu Wun; Chim, Yu Ning; Wong, Ronald Wong Man-Yeung; Cheung, Wing Hoi

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Patrick Haubruck University of Heidelberg, Department of Orthopaedics and Traumatology, HTRG- Heidelberg Trauma Research Group, Germany Raymond Purves Research Laboratory, Institute of Bone and Joint Research, University of Sydney, Australia
<b>REVIEW RETURNED</b>	03-Apr-2020

<b>GENERAL COMMENTS</b>	<p>The authors present the study protocol for a RCT investigating the influence of LMHFV on BMD in elderly patients that are wheelchair bound. All in all the subject is interesting and the application has potential for benefitting especially elderly disabled patients. Thus, I have read the protocol with great interest. All in all the study was well designed and the manuscript well prepared. However, I do have some major concerns and questions and I believe addressing these concerns and questions will improve the quality of the protocol and study substantially.</p> <p>Major concerns:</p> <p>1) The authors state that patients that are unable to stand and walk independently will be excluded from the study. Patients that are fully wheelchair bound have very limited ways of improving physical activity and BMD is generally low. Fragility fractures of the vertebrae happen in these patients as well. Thus, I believe it would be important to investigate the influence of the treatment on these patients as well. Maybe as a second study or a second group to the current study. I believe these patients could benefit massively from the treatment and excluding them shouldn't be the goal of the study. The authors could use the same study design and recruitment mechanism to recruit these patients as well and use BMD analysis, handgrip strength as well as SF36 as outcome. I strongly recommend to consider including them into the study.</p> <p>2) Will the groups be stratified? We all know, that gender plays an important role in the pathogenesis of osteoporosis, while age changes bone biology and muscle biology. Furthermore, BMI has implications on how our muscles recover and the entire metabolism is different in obese people. In my opinion, stratification for gender, BMI and age is important to achieve</p>
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	<p>comparable groups and results. Otherwise substantial differences in groups are a potential source for major bias.</p> <p>3) The authors state that assessment will be performed at baseline and at 6 months. In my opinion, it would be very interesting to include another assessment after 1 year and maybe even after 2 years two assess if LMHFV has a lasting effect or is only effective during the duration of the treatment. In order to reduce the radiation these long term assessment could only utilise the functional tests.</p> <p>4) Physical activity influences the BMD and muscle strength. How do the authors control for any unwanted additional physical activity of the subjects? If a person walks a lot at home, compared to another that only sits in the wheelchair, although being physically capable of walking, this would influence the outcome of the study in a major way. In my opinion, an elegant fix to that problem is supplying the participants with step counters. They are cheap and easily available and the authors could identify outliers in physical activity.</p> <p>5) What is the control therapy during this time? Will the participants get any other way of physical activity? This needs to be better described.</p> <p>6) Please include a paragraph regarding potential adverse events and potential risk for patients and explain why the benefits outweigh the risk.</p> <p>Minor concerns:  1) Page 7 line 1: Please correct and revise the sentence.  2) Page 7 line 9-10: Please correct and revise the sentence.  3) In my opinion the authors should say participants rather than subjects. Although this is a personal preferences, in my opinion, participants sounds much more humane and better.</p>
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<b>REVIEWER</b>	Danúbia de Sá-Caputo Universidade do Estado do Rio de Janeiro, Brazil
<b>REVIEW RETURNED</b>	25-May-2020

<b>GENERAL COMMENTS</b>	Congratulations to the authors for the subject of this manuscript.
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<b>REVIEWER</b>	Ditte Beck Jepsen Geriatric Research Unit, Department of Geriatric Medicine, Odense University Hospital, Odense, Denmark; Department of Clinical Research, University of Southern Denmark, Odense, Denmark
<b>REVIEW RETURNED</b>	17-Sep-2020

<b>GENERAL COMMENTS</b>	<p>Thank you for giving me the opportunity to review this manuscript. I have done it with great interest. Minor problems: although this reviewer thinks that there is great potential behind this concept of the study and is of interest to readers and public health professionals. One concern is the short follow up looking at BMD at 6 months follow-up as primary outcome. This reviewer considers that authors may need to</p> <p>Page 1 Introduction, line 6, 9, and 15  Please use the wording older adults instead of elderlies throughout the manuscript.</p>
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	<p>Page 4 Introduction line 8 Please use the wording older adults instead of elderly people, throughout the manuscript.</p> <p>Page 4-5line 20-3 Please consider rephrasing to make it more clear what is known and what is the missing gap. Are there no studies in older adults with walking disabilities? Or are there no studies with older adults using wheelchairs?</p> <p>Page 5 Methods and analysis. Study design Please insert a date for the study.</p> <p>Page 7, assessments line 6-11 Please describe in more detail how adverse events are recorded, and if and how the fall rates are obtained in both groups.</p> <p>Page 7, Intervention line 12 Please comment on the choice of unsupervised training and the adherence measurements. How is it planned to use the adherence measurements in the analysis?</p> <p>Page 10 Data analysis Please include a more detailed description of the planned analyses, intent to treat and/or per protocol. It would be valuable to include a description of the handling of missing data, and how to handle non normal distributed data. The authors should consider making a statistical analysis plan.</p> <p>Page 12-13 discussion It may be discussed if a longer follow-up period would have useful to see whether the possible treatment effects were maintained.</p>
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### VERSION 1 – AUTHOR RESPONSE

#### Reviewer 1

Comment	Response	Changes
Will the groups be stratified? We all know, that gender plays an important role in the pathogenesis of osteoporosis, while age changes bone biology and muscle biology. Furthermore, BMI has implications on how our muscles recover and the entire metabolism is different in obese people. In my opinion, stratification for gender, BMI and age is important to achieve comparable groups and results. Otherwise substantial differences in groups are a potential source for major bias.	Thank you for your comments and we agree that gender, BMI and age do play important roles and we agree that including the stratification for these factors would reduce potential bias. Statistical plan is revised to reflect this change.	P.11, line 1.
The authors state that assessment will be performed at baseline and at 6 months. In my opinion, it would be very interesting to include another assessment after 1 year and maybe	Thank you very much for your comments. The “lasting” treatment effect of LMHFV has previously been reported in our publication [32] to show improvements in	P.13, line 19 to 22.

<p>even after 2 years two assess if LMHFV has a lasting effect or is only effective during the duration of the treatment. In order to reduce the radiation these long term assessment could only utilise the functional tests.</p>	<p>muscle performance after 12 months of treatment cessation. Considering the additional visits to the hospital for assessment after six months may incur additional costs not originally approved by the funding body, particularly during COVID period that may put patients at risk. It would be more appropriate to leave this part out of the protocol. Relevant discussion has been added to acknowledge this point.</p>	
<p>Physical activity influences the BMD and muscle strength. How do the authors control for any unwanted additional physical activity of the subjects? If a person walks a lot at home, compared to another that only sits in the wheelchair, although being physically capable of walking, this would influence the outcome of the study in a major way. In my opinion, an elegant fix to that problem is supplying the participants with step counters. They are cheap and easily available and the authors could identify outliers in physical activity.</p>	<p>Thank you for this interesting suggestion. The research team is implementing this tool in another study on healthy mobile participants<sup>1</sup>. As participants in this study would deem to be frailer with very limited mobility. It would be financially not feasible to use step counters for this study due to limited resources. Thus the authors decides to not add this to the protocol. To deal with this potential problem, we will keep monitoring their activity level monthly, which is supplemented in the revised manuscript.</p>	<p>P.8, line 7.</p>
<p>What is the control therapy during this time? Will the participants get any other way of physical activity? This needs to be better described.</p>	<p>No specific physical activity or treatment will be given to the control group. It is clarified again in the manuscript.</p> <p><i>“... control group are instructed to maintain their habitual lifestyle without vibration treatment nor specific instructions given to take on additional physical exercise.”</i></p> <p>No-treatment control was adopted in many vibration studies, including our previous studies<sup>2</sup>.</p>	<p>P.8, line 5 to 7.</p>
<p>Please include a paragraph regarding potential adverse events and potential risk for patients and explain why the benefits outweigh the risk.</p>	<p>Thanks for pointing this out, the following is added to the <i>Interventions</i> section in the Methods.</p> <p><i>“No known side effects are associated ... risks of falling could</i></p>	<p>P.7, line 16 to 20.</p>

	<i>be minimized with the help of the on-site researchers.</i>	
Minor concerns: 1) Page 7 line 1: Please correct and revise the sentence.	The sentence is revised.	P.7, line 2.
2) Page 7 line 9-10: Please correct and revise the sentence.	The sentence is revised.	P.7, line 11-13.
3) In my opinion the authors should say participants rather than subjects. Although this is a personal preferences, in my opinion, participants sounds much more humane and better.	All “subject(s)” are replaced with participants.	Throughout the manuscript.

### Reviewer 2

Comment	Response	Changes
Congratulations to the authors for the subject of this manuscript	Thank you!	N/A

### Reviewer 3

Comment	Response	Changes
Thank you for giving me the opportunity to review this manuscript. I have done it with great interest. Minor problems: although this reviewer thinks that there is great potential behind this concept of the study and is of interest to readers and public health professionals. One concern is the short follow up looking at BMD at 6 months follow-up as primary outcome.	The discussion on the short follow-up time is supplemented in the final remarks.	P.13, line 19 to 22.
This reviewer considers that authors may need to Page 1 Introduction, line 6, 9, and 15 Please use the wording older adults instead of elderlies throughout the manuscript.	Thanks for the suggestion and all of the “elderlies” in the entire manuscript have been replaced with “older adults”.	Throughout the manuscript.
Page 4 Introduction line 8  Please use the wording older adults instead of elderly people, throughout the manuscript.	Same as above.	Same as above.

<p>Page 4-5 line 20-3</p> <p>Please consider rephrasing to make it more clear what is known and what is the missing gap. Are there no studies in older adults with walking disabilities? Or are there no studies with older adults using wheelchairs?</p>	<p>Thank you for pointing out the problem. The sentence has been revised.</p>	<p>P.5, line 1 to 4.</p>
<p>Page 5 Methods and analysis. Study design Please insert a date for the study.</p>	<p>The expected start and end dates are supplemented.</p>	<p>P.5, line 19 to 20.</p>
<p>Page 7, assessments line 6-11</p> <p>Please describe in more detail how adverse events are recorded, and if and how the fall rates are obtained in both groups.</p>	<p>The events will be recorded on a calendar provided to each participant to record the date and event details. This protocol was used in our previous study <sup>2</sup>.</p>	<p>P.7, line 12 to 13.</p>
<p>Page 7, Intervention line 12</p> <p>Please comment on the choice of unsupervised training and the adherence measurements. How is it planned to use the adherence measurements in the analysis?</p>	<p>The participants recruited in our local community settings to join this study are frailer in terms of mobility, and they are receiving the treatment within the institution. Therefore, it would be safer for the participants to receive the treatment under supervision. Compliance or adherence will be recorded both digitally by the treatment device in an SD card and manually by a calendar assisted by the staff, that is reported by the end of the study.</p>	<p>P.7, line 10.</p>
<p>Page 10 Data analysis</p> <p>Please include a more detailed description of the planned analyses, intent to treat and/or per protocol. It would be valuable to include a description of the handling of missing data, and how to handle non normal distributed data. The authors should consider making a statistical analysis plan.</p>	<p>Thank you for the suggestion. The additional statistical analysis methods have been added to the data analysis plan.</p>	<p>P.10, line 18 to 20.</p>
<p>Page 12-13 discussion</p> <p>It may be discussed if a longer follow-up period would have useful to see whether the possible treatment effects were maintained.</p>	<p>A 6-month study period was due to limited research resources and also considering the conditions of the research participants. We believe the treatment or beneficial effects should last based for at least 1 year after cessation of the vibration treatment that is supported by our</p>	<p>P.13, line 19 to 22.</p>

	previous study [32]. The discussion is added to the end of our final remarks.	
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1. Chow SK, Chim YN, Cheng KY, et al. Elastic-band resistance exercise or vibration treatment in combination with hydroxymethylbutyrate (HMB) supplement for management of sarcopenia in older people: a study protocol for a single-blinded randomised controlled trial in Hong Kong. *BMJ open* 2020;10(6):e034921. doi: 10.1136/bmjopen-2019-034921 [published Online First: 2020/07/02]
2. Leung KS, Li CY, Tse YK, et al. Effects of 18-month low-magnitude high-frequency vibration on fall rate and fracture risks in 710 community elderly--a cluster-randomized controlled trial. *Osteoporos Int* 2014;25(6):1785-95. doi: 10.1007/s00198-014-2693-6 [published Online First: 2014/03/29]

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Patrick Haubruck Raymond Purves Bone and Joint Research Lab, Kolling institute of Medical Research, The University of Sydney
<b>REVIEW RETURNED</b>	Patrick Haubruck Raymond Purves Bone and Joint Research Lab, Kolling institute of Medical Research, The University of Sydney

<b>GENERAL COMMENTS</b>	The authors have addressed my concerns sufficiently. The quality of the manuscript has improved substantially. No further comments
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<b>REVIEWER</b>	Ditte Beck Jepsen Department of Geriatric Medicine, Odense University Hospital, Denmark Institute of Clinical Research, University of Southern Denmark, Denmark
<b>REVIEW RETURNED</b>	06-Nov-2020

<b>GENERAL COMMENTS</b>	Congratulations to the authors
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